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2.	TITLE-ABSTR-KEY(crf) and TITLE-ABSTR-KEY(depression anxiety) *[All Sources(- All Sciences -)]*	62
1.	TITLE-ABSTR-KEY(crf) and TITLE-ABSTR-KEY(depression) *[All Sources(- All Sciences -)]*	396

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62 Articles Found

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The Journal Of Endocrinology
Volume 160, Issue 1 , January 1999, Pages 1-12
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The role of corticotropin-releasing factor in depression and anxiety disorders

Arborelius, L; Owens, M J; Plotsky, P M; Nemeroff, C B

Laboratory of Neuropsychopharmacology, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia 30322, USA

Abstract

Corticotropin-releasing factor (CRF), a 41 amino acid-containing peptide, appears to mediate not only the endocrine but also the autonomic and behavioral responses to stress. Stress, in particular early-life stress such as childhood abuse and neglect, has been associated with a higher prevalence rate of affective and anxiety disorders in adulthood. In the present review, we describe the evidence suggesting that CRF is hypersecreted from hypothalamic as well as from extrahypothalamic neurons in depression, resulting in hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and elevations of cerebrospinal fluid (CSF) concentrations of CRF. This increase in CRF neuronal activity is also believed to mediate certain of the behavioral symptoms of depression involving sleep and appetite disturbances, reduced libido, and psychomotor changes. The hyperactivity of CRF neuronal systems appears to be a state marker for depression because HPA axis hyperactivity normalizes following successful antidepressant treatment. Similar biochemical and behavioral findings have been observed in adult rats and monkeys that have been subjected to early-life stress. In contrast, clinical studies have not revealed any consistent changes in CSF CRF concentrations in patients with anxiety disorders; however, preclinical findings strongly implicate a role for CRF in the pathophysiology of certain anxiety disorders, probably through its effects on central noradrenergic systems. The findings reviewed here support the hypothesis that CRF receptor antagonists may represent a novel class of antidepressants and/or anxiolytics. [Journal Article, Review; 112 Refs; In English; England]

CAS Registry Numbers: Receptors, Corticotropin-Releasing Hormone; 9015-71-8, Corticotropin-Releasing Hormone

Citation Subset Indicators: Index Medicus

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Grant ID: MH-42088, Acronym: MH, Agency: NIMH;
Grant ID: MH-50113, Acronym: MH, Agency: NIMH

MeSH Terms: Adult; Animals; Anxiety Disorders, drug therapy (DT), * metabolism (ME); Child, Preschool; Corticotropin-Releasing Hormone, * physiology (PH); Depression, drug therapy (DT), * metabolism (ME); Disease Models, Animal; Humans; Hypothalamo-Hypophyseal System, physiology (PH); Infant; Maternal Deprivation; Neurons, physiology (PH); Pituitary-Adrenal System, physiology (PH); Rats; Receptors, Corticotropin-Releasing Hormone, antagonists & inhibitors (AI); Research Support, U.S. Gov't, P.H.S.; Stress, Psychological

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1: J Neural Transm Suppl. 2003;(64):17-34. Related Articles, Links

The role of peptides in treatment of psychiatric disorders.

Holsboer F.

Max Planck Institute of Psychiatry, Munich, Federal Republic of Germany. holsboer@mpipsykl.mpg.de

About 25 years ago the observation that neuropeptides serve as signalling molecules in the nervous system generated great expectations for drug industry. In this article the progress made since then in exploiting neuropeptide systems pharmacologically in psychiatry is highlighted. In affective disorders a number of neuropeptides seem to be causally involved in development and course of illness, especially corticotropin releasing hormone (CRH), vasopressin (AVP) and substance P, whose receptors are now targeted with small molecules designed to reduce depressive and anxiety symptoms. Although not exactly neuropeptides, also neurotrophins, may have a distinct role in antidepressant action and possibly also in causation of depression. Schizophrenia-like symptoms are caused by neurotensin (NT), supporting the notion that drugs interfering with NT systems are potential antipsychotics. Finally, sleep disorders, currently treated with hypnotics, that have serious adverse effects can be targeted with neuropeptides. According to the work by Axel Steiger several neuropeptides even if peripherally administered produce improvements of quality of sleep. All these observations call for intensified application of novel research tools necessary to exploit the potential of neuropeptide systems as psychopharmaceutical targets.

Publication Types:
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PMID: 12830927 [PubMed - indexed for MEDLINE]

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ELSEVIER FULL-TEXT ARTICLE

Functional characteristics of CRH receptors and potential clinical applications of CRH-receptor antagonists.

Grammatopoulos DK, Chrousos GP.

Sir Quinton Hazell Molecular Medicine Research Centre, Dept of Biological Sciences, The University of Warwick, Coventry, UK CV4 7AL. dgrammatopoulos@bio.warwick.ac.uk

Corticotropin-releasing hormone (CRH) plays a major role in coordinating the behavioral, endocrine, autonomic and immune responses to stress. CRH and CRH-related peptides and their receptors are present in the central nervous system and in a wide variety of peripheral tissues, including the immune, cardiovascular and reproductive systems, and have been associated with the pathophysiology of many disease states. These observations have led to the development of several CRH receptor type-selective antagonists, which have been used experimentally to elucidate the role of CRH and related peptides in physiological and disease processes, such as anxiety and depression, sleep disorders, addictive behavior, inflammatory and allergic disorders, neurological diseases and pre-term labor. Because of the complex network of multiple CRH receptor subtypes and their tissue- and agonist-specific signaling diversity, antagonists need to be developed that can target specific CRH receptor isoform-driven signaling pathways.

Publication Types:
- Review

PMID: 12431840 [PubMed - indexed for MEDLINE]

Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression

Johannes MHM Reul* and Florian Holsboer

Corticotropin-releasing factor (CRF) and its related family members are implicated in stress-related disorders such as anxiety and depression. Recently, two new members of this neuropeptide family have been discovered in the brain: urocortin II (also known as stresscopin-related peptide) and urocortin III (also known as stresscopin). These urocortins are selective agonists for the CRF_2 receptor, show a distinct neuroanatomical localization and are involved in stress-coping responses such as anxiolysis. Thus, CRF, the urocortins and their receptors form an intricate network in the brain involved in the acute phase as well as the recovery phase of the stress response.

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Abbreviations

ACTH	adrenocorticotrophic hormone
BNST	bed nucleus of the stria terminalis
CRF	corticotropin-releasing factor
CRFBP	non-receptor CRF-binding protein
CSF	cerebrospinal fluid
EW nucleus	Edinger-Westphal nucleus
GR	glucocorticoid receptor
HPA axis	hypothalamic-pituitary-adrenocortical axis
i.c.v.	intracerebroventricular
iLS	intermediate LS
LS	lateral septal nucleus
MR	mineralocorticoid receptor
PVH	paraventricular hypothalamic nucleus
Ucn	urocortin
VMH	ventromedial hypothalamic nucleus

Introduction

Anxiety and major depressive disorders are the most prominent stress-related psychiatric disorders and they impair the lives of approximately 10–15% of the population. For decades, the success of pharmacological treatment of these disorders has been dampened by various factors, including long latency of clinical effect, treatment resistance, adverse side effects, and, in the case of the anxiolytic benzodiazepines, tolerance and addictive potential. Although the themes of stress, anxiety and other stress-related disorders have been a topic of investigation continuously since the 1940s, antidepressant and anxiolytic drugs that are currently prescribed stem from the 1950s and are based on pharma-cological interaction with the classic neurotransmitters.

In 1981 a new era began: corticotropin-releasing factor (CRF) was discovered as the principal mediator of the effects of stress on the hypothalamic-pituitary-adrenocortical axis (HPA axis) and behavior [1]. Not surprisingly, clinical studies soon demonstrated that this neuropeptide is implicated in depression and anxiety disorders [2–5]. Basic research studies also presented evidence that elevated central CRF levels are involved in the etiology of stress-related physiological and behavioral disorders [6]. For the pharmacology field, the discovery of two CRF receptors and a non-receptor CRF-binding protein (CRFBP) was an immense breakthrough. With the recent discovery of more (endogenous) ligands beside CRF, the concept is dawning that CRF, its congeners and their receptors form an intricate network in the brain that potentially provides a variety of targets for drug intervention. In this review, we describe recent findings on the properties of CRF_1 and CRF_2 receptors and their ligands in the brain. Based on these exciting developments, we depict a new concept of the role of CRF_1 and CRF_2 receptors and their ligands in both the acute and recovery phase of the stress response. This concept is also presented as a framework for the pathophysiology of anxiety and major depressive disorders.

CRF and its receptors: a growing family

The CRF family of neuropeptides has undergone considerable expansion during recent times. Until recently, together with CRF, the family comprised structurally-related peptides including urocortin (Ucn) [7], fish urotensin I [8] and amphibian sauvagine [9]. The biological actions of CRF and Ucn are mediated via two types of G-protein-coupled receptors, CRF_1 and CRF_2, which have different expression patterns and physiological functions [10–12]. Two different splice variants of CRF_2 have been identified, $CRF_{2\alpha}$ and $CRF_{2\beta}$, which presented an uneven distribution between the brain (predominantly expressing $CRF_{2\alpha}$) and periphery (predominantly expressing $CRF_{2\beta}$) in rodents [13].

Whereas CRF is relatively selective for CRF_1 over CRF_2 receptors, Ucn is bound by both CRF_1 and CRF_2 with high affinity ([10,11]; see Table 1). The question remained whether a neuropeptide existed that would selectively bind to CRF_2 receptors. This question was answered by the recent discovery of two selective ligands for CRF_2, Ucn II (also known as stresscopin-related peptide) [14••,15••] and Ucn III (also called stresscopin) [15••,16••] (Table 1). Neither Ucn II nor Ucn III binds to CRFBP [16••], whereas CRF and Ucn do.

Thus, in mammalian brain, the CRF/Ucn receptor network comprises two receptor types and four ligands of which three (CRF, Ucn II, Ucn III) are pharmacologically monogamous and one (Ucn) is, at least regarding CRF_1 and CRF_2, promiscuous. This network of CRF/Ucn and their receptors receptors is further complicated by the

Table 1

Binding properties and functional activities of members of the CRF neuropeptide family.

Peptide	Binding (K_i, nM)			cAMP generation (EC_{50}, nM)		
	$hCRF_1$	$rCRF_{2\alpha}$	$mCRF_{2\beta}$	$hCRF_1$	$rCRF_{2\alpha}$	$mCRF_{2\beta}$
CRF (rat/human)	3.3	42	47	4	20	–
CRF (sheep)	1.1	230*	320*	–	–	–
Ucn (rat)	0.32	2.2	0.62	0.15	0.063	0.087
Ucn (human)	0.4	0.3*	0.5*	–	–	–
Ucn II (human)	>100	1.7	0.50	>100	0.26	0.42
Ucn II (mouse)	>100	2.1	0.66	>100	0.14	0.05
Ucn III (human)	>100	21.7	13.5	>100	0.16	0.12
Ucn III (mouse)	>100	5.0	1.8	>100	0.073	0.081
Urotensin I (fish)	0.4	1.8*	5.7*	–	–	–
Sauvagine (frog)	0.7	0.5*	2.1*	–	–	–

Data were taken from [10,11,16••,79]. Values were determined using transiently transfected COS-M6 cells (h/rCRF only), transiently or stably transfected mouse Ltk cells (h/rCRF receptors only), or stably transfected Chinese hamster ovary cells (cAMP measurements) or their membranes (binding experiments). *Binding experiments were conducted with α- and β-splice variant of the human CRF_2 receptor. For more details, see the text for references. (–), data not available; hCRF, human CRF; mCRF, mouse CRF; rCRF, rat CRF.

presence of the CRFBP binding protein that presumably constrains the biological activity of CRF and Ucn [17].

CRF_1 and CRF_2 in the brain: who and where are your ligands?

Receptor distribution

As revealed by *in situ* hybridization histochemistry studies, CRF_1 and CRF_2 mRNA show a distinct but overlapping distribution in the brain (Figure 1a; [12,18,19•,20•]). CRF_1 is widely distributed in central nervous system regions involved in sensory information processing and motor control, whereas CRF_2 is virtually restricted to subcortical structures (Figure 1a). Moderate levels of both receptors are expressed in the dorsal and median raphe nuclei, whereas only low levels are found in the paraventricular hypothalamic nucleus (PVH) [12,18,19•,20•]. Outside the brain, in the anterior pituitary, the CRF_1 receptor mediates the effects of CRF on adrenocorticotrophic hormone (ACTH) release and, thus, on glucocorticoid hormone secretion (Figure 1a; [10,20•]).

Ligand distribution

Ucn

A discrepancy has been found between the localization of Ucn-immunoreactive fibers and CRF_2 distribution. Brain nuclei most richly endowed with Ucn mRNA (i.e. the Edinger-Westphal nucleus [EW nucleus], lateral olivary and supraoptic nuclei; Figure 1b) mainly project caudally, despite high concentrations of CRF_2 receptors in forebrain areas such as the bed nucleus of the stria terminalis (BNST), lateral septal nucleus (LS), and the ventromedial hypothalamic nucleus (VMH) [18]. However, an Ucn-immunoreactive projection stemming from the EW nucleus was found to terminate in the intermediate LS (iLS) [18], but the projection ended in a region medially localized from the ventrolateral region to which CRF_2 is confined [19•]. With the recent discovery of the CRF_2-selective ligands Ucn II and Ucn III, answers can now be found to the question: where are the endogenous ligands for forebrain CRF_2?

Ucn II

Ucn II mRNA shows a distinct subcortical distribution including regions known to be involved in physiological and behavioral responses to stress such as the PVH (HPA axis and autonomic control [21]), the locus coeruleus (arousal and anxiety [22]) and the arcuate nucleus (food intake and energy balance [23]), and partly overlaps with the expression of CRF (in the PVH; [24]) and Ucn (in the brainstem and spinal motor nuclei [18]) (Figure 1b). After intracerebroventricular (i.c.v.) injection of Ucn II, Fos induction was observed in the BNST, PVH, central nucleus of the amygdala, parabrachial nucleus and nucleus tractus solitarii (NTS), but was absent in other CRF_2-rich locations such as the LS, raphe nuclei and VMH [14••]. Given the high affinity of Ucn II for CRF_2, the latter observation is unexpected and a solid explanation is still lacking. The incongruence might point to the need of additional factors required for activation of the neuron, at least in terms of Fos. Alternatively, these CRF_2-expressing neurons might display activation of signal transduction pathways that do not ultimately lead to synthesis of Fos. For instance, we have shown recently that phosphorylation of CREB (cAMP response element binding protein), a transcription factor activated through CRF_1 and CRF_2, is not necessarily correlated with Fos expression (A Bilang-Bleuel, J Rech, F Holsboer, JMHM Reul, unpublished data). Nevertheless, given the apparent resemblance

between the localizations of Ucn II and CRF, it seems pertinent that Ucn II participates in responses to stress [14••]. However, their differential binding preference for CRF_1 and CRF_2 suggests that CRF and Ucn II have different functions in the stress response.

Ucn III

The localization of Ucn III in brain (Figure 1b; [15••,16••]) is distinct from that of CRF [24], Ucn [18] and Ucn II [14••]. This most recently discovered member of the CRF neuropeptide family is found in the median preoptic area, the rostral perifornical area (a region lateral from the PVH), the posterior part of the BNST, and the medial nucleus of the amygdala [16••]. To date, unfortunately, no Fos studies have been performed with Ucn III. Of interest though is that parts of the perifornical region project to the LS (a CRF_2-rich region), an area in which immunoreactivity for both Ucn and piscine urotensin I can be found [18]. Within the LS, however, Ucn and urotensin I are differentially localized: Ucn-immunoreactivity is prevalent in the medial aspect of the iLS, whereas urotensin I-immunoreactivity is concentrated in the ventrolateral aspect of this nucleus (the site where CRF_2 mRNA is also found; see sections on receptor and ligand distribution). It can be speculated that, given the structural relationship between urocortins and urotensin, the immunoreactivity in the ventrolateral aspect of the iLS as revealed with the piscine urotensin I antiserum might actually be Ucn III. Indeed, Ucn-III-immunoreactive fibers have recently been found in this region of the LS (and in the VMH), which align well with the sites of CRF_2 mRNA expression (PE Sawchenko, personal communication).

The role of CRF_1 and CRF_2 receptors in stress processes

During the past few years, many studies have been conducted to discern the roles of CRF_1 and CRF_2 receptors in stress-related physiological and behavioral processes to gain insight into anxiety and major depressive disorders. Various strategies have been employed, including pharmacological approaches, mutant mice with functional deletions in the receptors and antisense oligodeoxynucleotide technology. These investigations have provided insight into the complex roles of CRF_1 and CRF_2 in the regulation of emotional behavior, HPA axis activity and autonomic function. For some processes the roles of CRF_1 and CRF_2 seem clear, whereas for others they still need to be resolved.

Anxiety and emotion

CRF_1

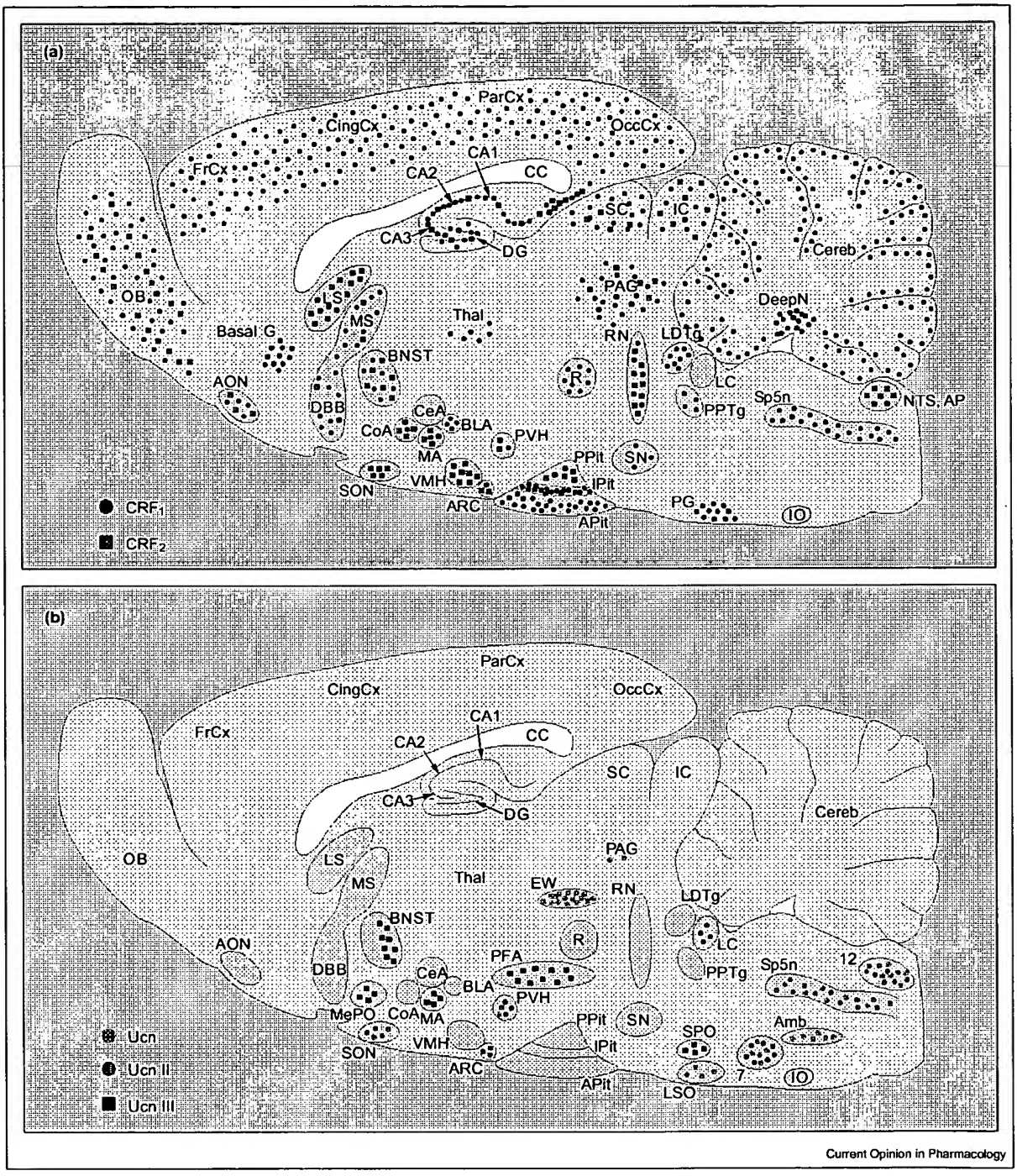
CRF plays an important role in the regulation of anxiety-related behavior and is implicated in anxiety and depressive disorders [25–27]. Several lines of evidence point to the participation of CRF_1 in mediating the effects of CRF. First, CRF_1, but not CRF_2, binds CRF with high affinity. Second, CRF_1-deficient mice show reduced anxiety-related behavior [28,29]. Third, transgenic mice overexpressing CRF show increased anxiety-related behavior ([30]; M van Gaalen, JMHM Reul, A Gesing, MP Stenzel-Poore, F Holsboer, T Steckler, unpublished data). Fourth, central administration of CRF_1 antisense oligodeoxynucleotides restrain CRF-evoked and social-defeat-evoked anxiety-related behaviors and elicit anxiolytic-like effects in certain anxiety tests, whereas CRF_2 antisense did not exert any significant effects in these tests [31–34]. Fifth, the selective (non-peptidergic) CRF_1 receptor antagonists NBI27914, CRA1000, CRA1001 (anilinpyrimidines), and CP154,526 (a pyrolopyrimidine) inhibit the anxiogenic action of CRF ([35,36]; for review see [37]). Anxiolytic effects have also been observed with the novel antagonists, R121919 (a phenylpirimidine; [38]), antalarmin (a pyrolopyrimidine derivative; [39,40]), DMP904 (a pyrazolopyrimidine) and DMP696 (a pyrazolotriazine) [41–43]. *In vivo* monitoring of the CRF_1 receptor in the living brain could soon become possible as a result of the recent accomplishments in the development of non-peptidergic CRF_1 ligands for single photon emission computed tomography (SPECT) and positron emission tomography (PET) [44,45]. This should reveal any changes in CRF_1 receptor expression that occur in emotional states.

CRF_2

Although there is robust evidence that CRF_1 is highly involved in anxiety-related behavior, a role for CRF_2 cannot be excluded. The three lines of CRF_2-deficient mice that have been described [46•–48•], unfortunately, do not provide a clear answer to the question about the role of this receptor in anxiety. In two lines of CRF_2-deficient mice, increased anxiety-related behavior was observed [47•,48•], whereas in the third no changes were found [46•]. This disparity could be caused by differences in genetic background, environmental factors and the behavioral test conditions used [49].

Recent pharmacological experiments, however, point to a much more complex involvement of the CRF_2 receptor in anxiety. The picture is emerging that activation of the CRF_2 receptor can result in anxiolysis or anxiogenesis depending on when the animal is tested and, possibly, where the receptor is localized. Radulovic and colleagues [50] observed that injection of a high (500 ng/mouse), CRF_2-binding, dose of human/rat CRF into the iLS of mice increases anxiety-like behavior in the plus-maze test 30 minutes after injection, which was prevented by pretreatment with the CRF_2 receptor antagonist anti-sauvagine-30. Increased anxiety in the plus-maze test was also observed 30 minutes after the mice had been immobilized for 60 minutes. This post-immobilization anxiety was prevented if the animals were treated intraseptically, but not intradorsohippocampally, with anti-sauvagine-30 before the stress procedure [50]. Thus, in the short term, CRF_2-mediated signaling in the iLS results in anxiogenesis. Physiologically, the CRF_2 receptor in this nucleus is likely to be activated by Ucn stemming from the EW nucleus [18] and, probably more so, by Ucn III from the perifornical region [16••] (PE Sawchenko, personal communication). However, i.c.v. administration of the selective CRF_2 receptor agonists mUcn II [51••] or mUcn III (EP Zorrilla, personal

Figure 1



communication) has no short-term effects but after four hours results in reduced anxiety-related behavior in the plus-maze test. Thus, CRF_2 in the brain is capable of reducing anxiety in a delayed fashion.

The anxiogenic and anxiolytic properties of CRF_2 are certainly not paradoxical, because they operate in different time domains after stress. Together, it can be postulated that during the acute (early) phase of the stress response

Figure 1 legend

Distribution of (a) CRF_1 and CRF_2 mRNA and (b) Ucn, Ucn II and Ucn III mRNA in a sagital section of the rodent brain. The presented mRNA distribution is based on *in situ* hybridization studies reported in [12,14••,16••,18,19•,20•,80]. The drawn sagital sections are only 2-dimensional schematic representations and, therefore, cannot be neuroanatomically exact. 7, facial nucleus; 12, hypoglossal nucleus; Amb, ambiguus nucleus; AON, anterior olfactory nucleus; AP, area postrema; Apit, anterior pituitary; ARC, arcuate nucleus; Basal G, basal ganglia; BLA, basolateral amygdala; CA1–3, fields CA1–3 of Ammon's horn, CC, corpus callosum; CeA, central nucleus of the amygdala; Cereb, cerebellum; CingCx, cingulate cortex; CoA, cortical nucleus of the amygdala; DBB, diagonal band of Broca; Deep N, deep nuclei; DG, dentate gyrus; FrCx, frontal cortex; IC, inferior colliculi; IO, inferior olive; IPit, intermediate pituitary; LC, locus coeruleus; LDTg, laterodorsal tegmental nucleus; LSO, lateral superior olive; MA, medial nucleus of the amygdala; MePO, median preoptic area; MS, medial septum; NTS, nucleus tractus solitarii; OB, olfactory bulb; OccCx, occipital cortex; PAG, periaquaductal gray; ParCx, parietal cortex; PFA, perifornical area; PG, pontine gray, PPit, posterior pituitary; PPTg, pedunculopontine tegmental nucleus; R, red nucleus; RN, raphe nuclei; SC, superior colliculi; SN, substantia nigra; SON, supraoptic nucleus; SP5n, spinal trigeminus nucleus; SPO, superior paraolivary nucleus; Thal, thalamus.

the increase in emotionality (anxiety) is evoked by CRF-mediated CRF_1 activation and Ucn- or Ucn-III-mediated CRF_2 activation, presumably in the amygdala, BNST and/or iLS. However, as part of the recovery phase CRF_2, following activation by Ucn, Ucn II and/or Ucn III, participates in reducing emotionality some hours after the stressful experience. Thus, CRF_2 has a dual mode of action on anxiety-related behavior. A challenge for the future will be to resolve the exact neural circuitry involved, the underlying molecular and cellular mechanisms, and the manner in which this dual action program is tuned by afferent neural input (e.g. from the frontal cortex, hippocampus, hypothalamus and autonomic centres) and humoral input (e.g. glucocorticoid hormones).

HPA axis regulation

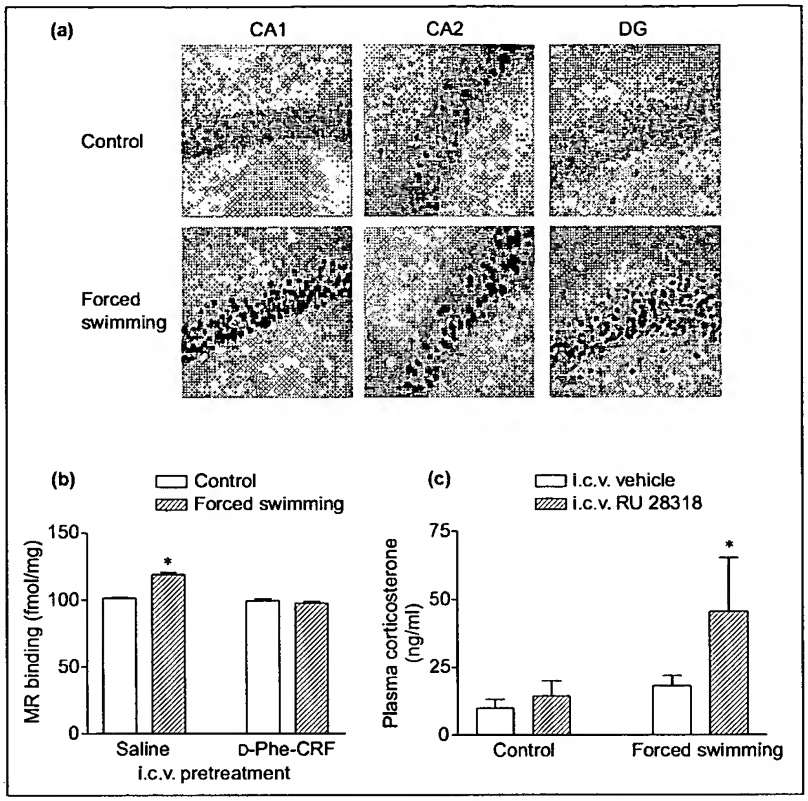
Disturbances in HPA axis regulation seem to play a profound role in the etiology of major depression [52•,53]. Moreover, studies on depressed patients have suggested that there is a close correlation between a stable remission of the clinical symptoms and a normalization of HPA regulation [54]. The cause for the aberrant — in most cases, hyperactive — HPA axis is thought to be a hyperactive central CRF system (for review, see [25,26,55–57]) and defunct brain and pituitary corticosteroid receptor systems [52•,58,59•]. More than a decade ago, a reduced CRF receptor density was found in the frontal cortex of depressed patients that had committed suicide [3]. Only recently have efforts been made to delineate CRF_1 and CRF_2 expression in post-mortem brains of depressed patients. In a recent study, investigators observed in pituitaries of suicide victims a shift in the ratio between CRF_1 (less) and CRF_2 (more) mRNA levels from normal levels, but it was unclear whether the victims had a history of major depressive illness [60]. Investigations into the role of CRF_1 and CRF_2 in HPA regulation have been mainly performed in rodents.

CRF receptors

Recent studies on CRF_1- and CRF_2-deficient mice indicate that these receptors play different roles in the HPA axis. CRF_1-deficient mice are unable to mount a stress-induced HPA response in terms of circulating ACTH and corticosterone, but their baseline ACTH levels are normal and baseline corticosterone levels virtually undetectable [28,29,61,62]. Thus, CRF_1 is crucial for stress-induced HPA responsiveness but not for the baseline hypothalamic-pituitary drive. In the PVH, only low levels of CRF_1 mRNA can be found but the levels of CRF_1 mRNA increase in response to stress [20•,63–66] or i.c.v. administration of CRF [67]. This induction of CRF_1 mRNA may be implemented in the positive feedback action of CRF on PVH neurons, but this needs to be further explored.

Exposure of the CRF_2-deficient and wild-type mice to restraint stress revealed changes in HPA axis regulation at different levels in two of the three mutant lines [46•–48•]. Kishimoto *et al.* [48•] observed no changes, presumably because they analysed HPA activity at a single time-point. The other two CRF_2-mutant mouse lines showed augmented responses in plasma ACTH and corticosterone levels to restraint stress [46•,47•]. The plasma ACTH levels in the mutant mice, however, decreased within 10 min of stress onset, earlier than in wild-type animals. Ten minutes after stress onset, the corticosterone levels continued to rise in the mutant mice, reaching higher levels than in the wild-type mice [46•,47•]. At 90 min after stress, corticosterone levels were still higher in the mutant mice than the wild-type mice. It is clear from these data that there is an array of changes in the HPA axis of CRF_2-mutant mice that could explain the different hormonal responses. First, hypersensitivity of the corticotrophic cells to hypothalamic secretagogues; second, the higher glucocorticoid levels cause ACTH levels to come down earlier, via higher negative feedback inhibition; and third, the adrenal cortex of the mutant mice may be hypersensitive to ACTH [46•,47•]. Overall, these changes in HPA responses to stress suggest that CRF_1 and CRF_2 receptors act in an antagonistic manner: such that CRF_1 activates and CRF_2 attenuates the stress response. The sites of these antagonistic actions are presently not known, but might include the pituitary gland, the PVH, brain areas providing afferent input to the PVH such as the amygdala, BNST and the LS, and the sympathetic motor nuclei driving the sympathoadrenomedullary pathway. Studies on the HPA axis of recently created mutant mice lacking both CRF_1 and CRF_2 receptors confirm the data obtained with the single gene mutants, although the CRF_1 receptor mutation has a

Figure 2



Effect of forced swim stress on rat hippocampal MR levels and its consequences for MR-mediated HPA axis regulation. **(a)** Forced swimming induces, within 24 hours, an increase in MR-immunoreactivity in nuclei of pyramidal and granular neurons in the CA1, CA2, CA3 (not shown) hippocampal pyramidal layers and the dentate gyrus (DG). This effect was stressor-specific, as it was also seen after novelty stress, but not after exposure to a cold environment (not shown). **(b)** I.c.v. pretreatment with the non-selective CRF receptor antagonist (D-Phe^{12},Nle^{21,38},α-Me-Leu^{37})-CRF$_{12-41}$ (D-Phe-CRH$_{12-41}$) prevented the forced-swimming-induced increase in hippocampal MRs. Moreover, i.c.v. CRF treatment mimics the effect of stress on hippocampal MR levels (not shown). **(c)** As shown in a RU 28318 challenge test, the forced-swimming-induced elevation in hippocampal MR levels is associated with a potentiated MR-mediated inhibition of HPA activity. RU 28318 is a selective MR antagonist and, after i.c.v. administration, releases the HPA axis from the tonic inhibitory control elicited by hippocampal MRs. The experiment was based on the idea that, when MRs are upregulated after stress, the release of HPA activity by RU 28318 would be exaggerated compared with the control, unstressed, situation. Thus, rats were stressed by forced swimming, injected i.c.v. with RU 28318 24 hours later and trunk blood was collected 30 min after injection. Indeed, the results show that the release of HPA activity in terms of plasma corticosterone levels was larger when rats had been stressed 24 hours earlier, indicating that the stress-induced increase in hippocampal MR levels is associated with an enhanced MR-mediated tonic inhibitory control of HPA axis activity. For further details, see [70••]. Reprinted, with permission, from [70••]; copyright 2001 by the Society for Neuroscience.

dominating influence, presumably because of its 'key' position on the anterior pituitary corticotrophic cells [68].

Corticosteroid receptors

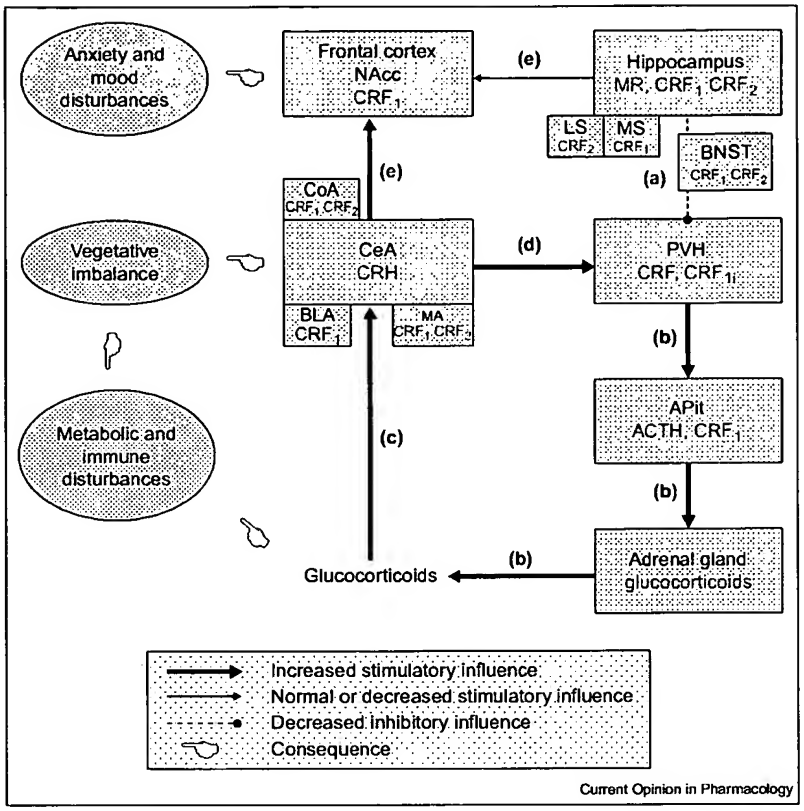
In addition to the CRF receptors, corticosteroid receptors are also key elements in the regulation of the HPA axis [58,59•]. They can be grouped into two types of corticosteroid-binding receptors: the mineralocorticoid receptor (MR or type I) and the glucocorticoid receptor (GR or type II) [69]. MRs are mainly localized in the hippocampus, whereas GRs have a widespread distribution in the central nervous system. They have different functions in HPA regulation, with MRs mediating the tonic inhibitory influence of the hippocampus (via the BNST) on parvicellular PVH neurons, and GRs mediating the negative feedback action of glucocorticoids on HPA activity [58,59•,69]. Recently, we discovered a new mechanism of cross-talk between the CRF neuropeptide systems and the hippocampal MRs. It was found that acute stressors act via a CRF receptor mediated action to cause, within eight hours after stress, an elevation in MR levels in the hippocampus, which was associated with an augmented MR-mediated inhibition of HPA activity (Figure 2; [70••]). Thus, CRF receptors are involved in strengthening an important control instrument (the MR) of the HPA axis. Although the effect of stress could be mimicked by an i.c.v. injection of CRF, pointing to an involvement of CRF [70••], exactly which CRF receptor mediates this phenomenon and where it is localized needs to be clarified. Furthermore, we have postulated that, given the eminent role of the CRF–MR pathway in maintaining control of HPA axis activity, in patients suffering from a stress-related disorder such as major depression, HPA hyperactivity might have developed as a result of MR induction becoming desensitized to CRF or CRF-like neuropeptides [59•,70••].

Summarizing, CRF_1 plays a critical role in the acute phase of the stress-induced HPA response, whereas CRF_2 is involved in the recovery phase. The stress-evoked increase in hippocampal MR expression appears to be part of the recovery phase but whether this element is mediated by CRF_1 or CRF_2 receptors needs clarification.

Significance for anxiety disorders and depression

An increased central CRF drive seems to be a feature often seen in major depression and anxiety disorders. This

Figure 3



Working hypothesis of limbic–HPA-axis interactions in anxiety and depressive disorders. On the basis of the presently established afferent and efferent regulatory interactions between the HPA axis and its limbic 'partners' (the hippocampus and the amygdala), we propose a framework giving a neuropharmacological basis to the psychiatric, neurovegetative and physiological disturbances seen in anxiety and depressive disorders. Patients suffering from major depression or pathological anxiety often show a dysregulated – mostly hyperactive – HPA axis, which is associated with increased CSF levels of CRF [26,55,56]. Apart from intrinsic HPA axis disturbances at the hypothalamic, pituitary or adrenal level, the reason for the HPA hyperactivity may well derive from defunct processes in the hippocampus and central nucleus of the amygdala (CeA) known to provide direct and indirect efferent projections to the PVH [59•,81]. As postulated (see text), chronic stressful life events result in a loss of capacity of CRF or CRF-related peptides to upregulate hippocampal MR levels, **(a)** leading to a loosening of the tonic inhibitory influence on parvicellular neurons in the PVH [59•]. In depressed patients and in a variety of animal models, a reduced expression of MR has indeed been found [58,59•,82].
(b) Consequently, levels of CRF and co-expressed vasopressin will increase in these neurons (for review, see [52•,57,59•]), providing an enhanced drive on HPA activity, CRF_1 receptor desensitization in the anterior pituitary (APit) and adrenal hyperplasia [52•,59•].
(c) Subsequently, the elevated circulating glucocorticoid levels will raise CRF expression in the CeA [72], **(d)** resulting in an enhanced stimulatory influence on the PVH. In this manner, a positive feed-forward loop develops, accelerating the establishment of a state of sustained HPA hyperactivity. Importantly, regarding the activity of the efferent amygdaloid and hippocampal projections to the nucleus accumbens (NAcc), **(e)** a shift may occur toward an augmented input from the CeA relative to that from the hippocampus. Such a shift will result in an increased emotionality that is likely to develop in subjects genetically vulnerable to pathological anxiety and mood disorders. Finally, the enhanced caudally directed CeA activity leading to an increased sympathetic outflow in combination with the excess glucocorticoid levels can result in a variety of neurovegetative (e.g. cardiovascular and gastrointestinal problems), metabolic and immune disturbances, often seen in anxiety, mood and psychosomatic disorders. Also, CeA-associated structures such as the cortical (CoA), basolateral (BLA) and medial (MA) amygdala, and hippocampus-associated structures such as the LS and medial septum (MS) are shown in the diagram (gray boxes) because they participate strongly in CeA and hippocampus functioning. In addition, their own function is modulated by incoming signals via CRF_1 and/or CRF_2 receptors. The BNST, containing both CRF_1 and CRF_2 receptors, is shown because it is an important relay station for hippocampal output to the PVH. Thus, this model can be used as a framework to investigate integratively the anxiogenic, anxiolytic, HPA-driving, HPA-restraining and other actions of CRH, Ucn, Ucn II and Ucn III. Such studies should also implement interactions of these neuropeptides with the classical neurotransmitters which, for the sake of clarity, were not depicted in the scheme. Other structures that may participate were also excluded; for instance, thalamic paraventricular nucleus, which contains low to moderate CRF_1 levels [20•,83]. Elucidating the interactions between the various components of this network will bring forward new pharmacotherapeutic strategies for the treatment of anxiety and depressive disorders. Yellow boxes show primary elements (brain regions and parts of the HPA axis) of the interactions between the limbic system and HPA axis. The different categories of pathological disturbances resulting from aberrant functioning of certain elements of the network are shown in pink ovals. The localization of CRF_1 is indicated in red and CRF_2 in blue; other important components, such as CRF, ACTH, glucocorticoids, and MR, are indicated in green. CRF_{1i}, CRF_1 mRNA expression that is inducible by stress or CRF.

notion stems from measurements of CRF levels in cerebrospinal fluid (CSF), CRF binding and CRF challenge tests [4,71]. Comparing a variety of studies revealed that elevated CRF in the CSF was not an equivocal finding in all studies but seemed to depend on certain factors associated with the depressive illness. In particular, those patients showing melancholia, psychosis, hypercortisolemia and dexamethasone non-suppression had elevated CSF CRF levels (for review, see [55,56]). It is presently still unclear from where in the brain the elevated levels of CRF are produced. It is, however, unlikely that they are derived exclusively from the PVH. The hypersecreted CRF may originate from the central nucleus of the amygdala, where it is known that synthesis of the neuropeptide is under

positive control of glucocorticoid hormones [72]. Thus, those depressed patients who hypersecrete glucocorticoids — at least in part as a result of defunct hippocampal inhibition of HPA activity (see previous section and Figure 3) — would also in turn increase their CRF synthesis in the central amygdaloid nucleus. Indeed, hypercortisolemia in depressed patients is associated with elevated CSF CRF levels. The increased expression of CRF in the central amygdaloid nucleus might be responsible for the increases in emotionality and anxiety, and the neurovegetative instability often associated with major depression [73,74]. Moreover, the central amygdaloid nucleus exerts, via its direct and indirect (via the BNST) connections to the PVH, a stimulatory influence on the HPA axis [59•]. We can speculate that in depressed patients a positive feed-forward loop might have established between the amygdala and the HPA axis. Given that the neural and humoral components of this loop have uncountable interactions with other — central and peripheral — systems, the consequences would be manifold, including effects on mood, cognition, libido, the cardiovascular system, immune system and metabolism (see Figure 3).

We postulated earlier that CRF_1 and CRF_2 receptors play different roles in stress-evoked anxiety, in which both receptors operate in different regions of the brain (e.g. central amygdaloid nucleus, BNST, iLS), in the acute (anxiogenic) phase of the stress response, and CRF_2 promotes anxiolysis during the stress recovery phase (see earlier section discussing the role of CRF_2 in anxiety and emotion). Also, we have described a parallel mechanism for the role of these receptors in the stress-induced HPA response. There are strong indications for a CRF-evoked CRF_1-mediated hypersignaling in the brain of patients suffering from anxiety and depressive disorders. This condition is thought to be responsible for the increases in emotionality, HPA activity and neurovegetative disturbances seen in these patients. Indeed, a first exploratory clinical study in our clinical department at the Max Planck Institute of Psychiatry (Munich, Germany) in which depressed patients were treated with the non-peptidergic CRF_1 receptor antagonist R1219191, showed that blocking CRF_1 signaling in these patients resulted in a substantial reduction in the depression and anxiety scores [75••]. The current status of research promises that CRF_1 receptor antagonists represent a novel pharmacotherapeutic strategy to treat depression, pathological anxiety (such as phobias and panic) and post-traumatic stress disorder. This recent development in the pharmacotherapy of mood and anxiety disorders is an important step toward the establishment of therapies based on scientific causality. It is more than likely that this development is also a significant step on the way to the ultimate goal of a pharmacotherapy with rapid onset of clinical effect, neglegible side effects and no treatment resistance

It is still possible that, in addition to CRF_1 hyperfunction, CRF_2 receptor hypofunction might exist in depressed patients. Due to an impaired CRF_2-mediated anxiolysis, the subject might remain in an extended state of anxiety and arousal. Other stress recovery processes may also be impaired by the reduced CRF_2 activity, including HPA regulation and autonomic processes [15••,46•–48•,76,77].

Figure 3 presents a working hypothesis based on an integration of the previously described issues. Our hypothetical model proposes that the development of anxiety and mood disorders is caused by a shift in the balance between the effects of the hippocampus and the central nucleus of the amygdala initially on the HPA axis, but eventually also on the nucleus accumbens and frontal cortex, which are brain regions involved in the regulation of affective states. The altered state of amygdaloid output is also expected to affect autonomic outflow which, in combination with the enhanced glucocorticoid secretion, could be responsible for the physiological, metabolic and immune disturbances often seen in depressed and anxious patients. The CRF neuropeptide family and its receptors are major participants in this network and with the recent growth of this family (i.e. Ucn II and Ucn III) a major step was made toward the elucidation of the roles of the CRF_1 and CRF_2 receptors in anxiety and depression.

Conclusions and perspectives

Overall, the blueprint of an intricate network controlling the acute and the recovery phase of the stress coping response is being drawn up. Recent advances — for example, the identification of new members of the CRF neuropeptide family, elucidating the dual function of CRF_1 and CRF_2 receptors in anxiety and HPA regulation and the CRF–MR regulatory shunt in HPA axis control — have provided the cornerstones enabling a significant leap in our understanding of the wiring and timing of the stress coping response. Of utmost importance is the acquired knowledge about the stress defense mechanisms underpinning anxiolysis, HPA control and autonomic stability.

These advances open the way for the development of novel classes of antidepressant drugs not just targeting the acute response systems but also acting supportively with regard to the stress defense mechanisms. To address this goal substantial investments are required to further elucidate the regulatory pathways and players governing the network in health and disease. With the recent development in the fields of functional genomics and pharmacogenomics (for instance, see [78••]) and proteomics, built on the experience of several decades of research in stress physiology, neuroanatomy, pharmacology and molecular biology, this ambitious plan can be mastered.

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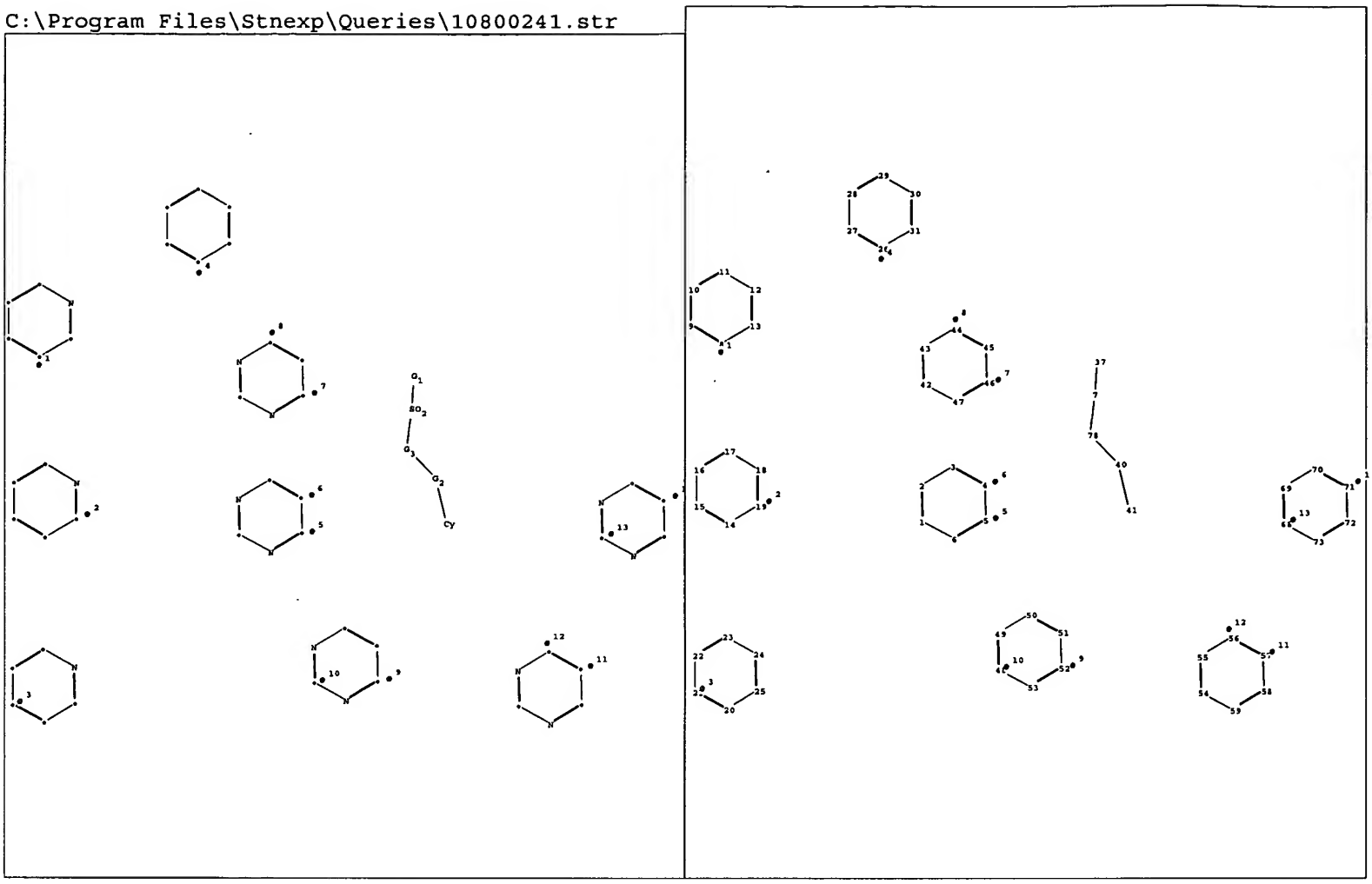

chain nodes :
7 37 40 41 78
ring nodes :
1 2 3 4 5 6 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
27 28 29 30 31 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59
68 69 70 71 72 73
chain bonds :
7-37 7-78 40-41 40-78
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13 14-15 14-19 15-16
16-17 17-18 18-19 20-21 20-25 21-22 22-23 23-24 24-25 26-27 26-31 27-28 28-29
29-30 30-31 42-43 42-47 43-44 44-45 45-46 46-47 48-49 48-53 49-50 50-51 51-52
52-53 54-55 54-59 55-56 56-57 57-58 58-59 68-69 68-73 69-70 70-71 71-72 72-73
exact/norm bonds :
7-37 7-78 40-41 40-78
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13 14-15 14-19 15-16
16-17 17-18 18-19 20-21 20-25 21-22 22-23 23-24 24-25 26-27 26-31 27-28 28-29
29-30 30-31 42-43 42-47 43-44 44-45 45-46 46-47 48-49 48-53 49-50 50-51 51-52
52-53 54-55 54-59 55-56 56-57 57-58 58-59 68-69 68-73 69-70 70-71 71-72 72-73
isolated ring systems :
containing 1 : 8 : 14 : 20 : 26 : 42 : 48 : 54 : 68 :

G1:[*1],[*2],[*3],[*4]

G2:CH2,NH

G3:[*5-*6],[*7-*8],[*9-*10],[*11-*12],[*13-*14]

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:Atom 9:Atom 10:Atom 11:Atom
12:Atom

13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:Atom 21:Atom
22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom
37:CLASS 40:CLASS 41:Atom 42:Atom 43:Atom 44:Atom 45:Atom 46:Atom 47:Atom 48:Atom
49:Atom 50:Atom 51:Atom 52:Atom 53:Atom 54:Atom 55:Atom 56:Atom 57:Atom 58:Atom
59:Atom 68:Atom 69:Atom 70:Atom 71:Atom 72:Atom 73:Atom 78:CLASS